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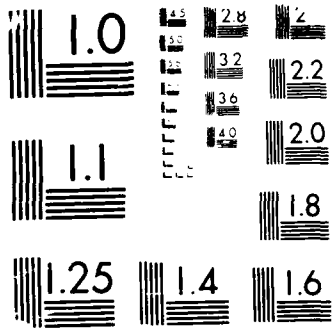


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# IMMUNE ALTERATION STUDIES IN IRRADIATED DOGS

C. A. Bowles
Immuquest Laboratories, Inc.
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Fairfax, VA 22031

31 October 1986

Technical Report



CONTRACT No. DNA 001-83-C-0172

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The objectives of this research work were to (1) serially evaluate the immune function of experimentally manipulated dogs to define the time required to normalize immune function; (2) identify immunologic lesions produced by the experimental protocol which causes a delay in recovery of immune function; and (3) define method of restoring immune function through the use of immune enhancing agents.

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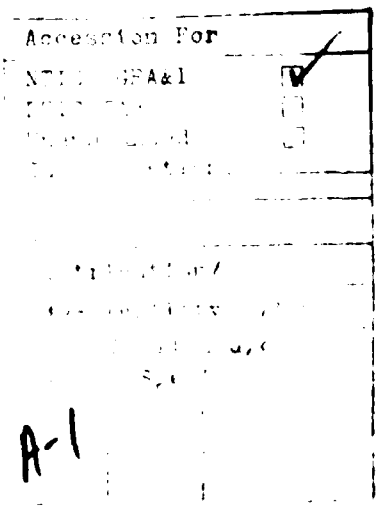
## PREFACE

This report presents progress achieved between August 1, 1983, through September 30, 1986, on Contract DNA001-83-C-0172, entitled "Immune Alteration Studies in Irradiated Dogs," for the Armed Forces Radiobiology Research Institute (AFRRI), Bethesda, Maryland. This contract was designed to provide information relating to the immune and inflammatory systems of dogs following experimental injury consisting of total body irradiation and *E. coli* sepsis. These experimental conditions were selected to mimic military situations, and the data generated on the project will assist in defining methods for health management of individuals exposed to these injuries in battlefield conditions.

Research was conducted according to the principles enunciated in the "Guide for the Care and Use of Laboratory Animals," prepared by the Institute of Laboratory Animal Resources, National Research Council.





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## SECTION 1

## OBJECTIVE AND SCOPE

The specific objectives of this three-year contract were to: (1) serially evaluate the immune function of experimentally manipulated dogs to define the time required to normalize immune function, (2) identify immunologic lesions produced by the experimental protocol which causes a delay in recovery of immune function, and (3) define methods of restoring immune function through the use of immune enhancing agents.

These overall objectives were accomplished by performing a series of assays of immune and inflammatory function as outlined below.

(a) Perform lymphoproliferative assays of T- and B-cell function.

(b) Perform assays of macrophage and neutrophil function, including studies of random and chemotactic migration, Fc mediated particle attachment and ingestion, and microbial kill.

(c) Perform mechanistic studies of immune suppression, including evaluation of T-suppressor and T-helper cell development.

(d) Perform assays to evaluate primary and secondary immune responses to T-cell and B-cell dependent antigens.

(e) Perform in vivo assays of immune function in an attempt to correlate with in vitro findings.

## SECTION 2

## EXPERIMENTAL DESIGN

### 2.1 ANIMAL MODELS.

Study animals consisted of adult male and female, beagle dogs purchased from a commercial source by AFRRI. The dogs were housed, quarantined and treated at AFRRI according to protocols designed by the Government's scientific staff. Approximately 125 dogs were studied during this contract period and consisted of animals receiving experimental manipulation of irradiation, surgical implant of a sterile fibrin clot or a fibrin clot containing *E. coli*. These insults were introduced either singly or in combination, as outlined in Table 1. Normal untreated dogs served as controls and were included with each set of treatment groups.

### 2.2 *IN VITRO* EVALUATION OF IMMUNE AND INFLAMMATORY FUNCTION.

Immune and inflammatory function studies were performed using heparinized whole blood collected from treated or control dogs on the day of test. The blood was transported to the testing laboratory and processed to isolate cellular elements of interest, including mononuclear cells (lymphocytes and macrophages) or polymorphonuclear leukocytes (neutrophils). The purified cells were assayed for functional activity, as summarized in Table 2. Individual dogs were tested sequentially starting pretreatment and on post-treatment days 1 through 50. Generally, dogs were tested twice each week for the first three weeks and then weekly thereafter. The test intervals and the animal model systems were defined by the Government's Study Team.

SECTION 3

RESULTS

## 3.1 STUDIES OF LYMPHOCYTE FUNCTION.

The lymphocyte proliferative response to the mitogens, concanavalin-A (Con-A) and pokeweed mitogen (PWM) were evaluated using dogs receiving 150 cGy irradiation (TBI) sterile fibrin clots (SC), fibrin clots containing $1 \times 10^9$ *E. coli* ($10^9$ EC), or a combination of these insults, i.e., TBI-SC or TBI-$10^9$ EC. Findings of these studies suggest that TBI transiently reduces lymphocyte blastogenesis during days 1-3 post-irradiation, and that responses return to normal thereafter. Compared to dogs receiving TBI only, dogs receiving TBI-SC had blastogenic responses significantly depressed on days 21 through 50 post-irradiation. In contrast, dogs receiving TBI-$10^9$ EC had blastogenic responses not significantly different than those of TBI only dogs. Single injuries of SC or $10^9$ EC produced transient changes in blastogenic activity without significant trends.

In a parallel set of experiments, the blastogenic activity of lymphocytes from dogs receiving TBI only were evaluated for response to Con-A at 3, 4, 5, and 7 days after lymphocyte cultures had been established. The data suggests that lymphocyte proliferation in irradiated dogs reached its peak response on day 5 of culture, while the blastogenic response of normal lymphocytes reached their peak response on day 3 of culture. These findings may suggest a shift in lymphocyte subpopulations, thereby delaying the onset of the blastogenic response. Alternatively, the accessory cell population (macrophages) may have been modified by the irradiation, thus impairing their ability to initiate the blastogenic response.

## 3.2 STUDY OF NEUTROPHIL FUNCTION.

Neutrophil function was evaluated in a series of dogs receiving TBI (150 cGy), SC, $10^9$ EC or a combination of these insults. Assays of neutrophil function included cell adherence to glass or to nylon wool, migration in agarose droplet (chemokinesis), membrane receptor expression (Fc receptors), particle ingestion, oxidative burst and microbial killing. The results of these studies can be summarized as follows:

### 3.2.1 Adherence - spontaneous glass or nylon wool adherence was not markedly changed by any of the treatments.

3.2.2 Fc Receptor Expression - Fc receptor expression was not markedly altered by any of the treatments.

3.2.3 Particle Ingestion - spontaneous particle (opsonized sheep erythrocytes) ingestion was not markedly altered by any of the treatments.

3.2.4 Random Migration - chemokinesis from agarose droplets were found to be markedly or significantly altered by the experimental manipulation. Among the changes in migration was a depressed migration by neutrophils from TBI (150 cGy) dogs, compared to control dog responses. Dogs receiving $10^9$ EC had significantly enhanced migration on post-implant days 1 through 7 before migration capabilities returned to pretreatment levels. Dogs receiving SC had migration responses similar but to a lessor magnitude, as was seen with EC dogs. The migration seen in dogs receiving TBI-EC and TBI-SC also showed enhanced migration. The migration seen in these dogs was less than seen in dogs receiving SC or EC alone. These data may suggest that irradiation reduces the capability of neutrophils to migrate, in addition to causing a marked reduction in numbers of these cells in the peripheral blood. The reduced migration may be due to a newly emerging population of cells which require further maturation before reaching maximum migration potential.

## 3.3 NEUTROPHIL FUNCTION IN CHEMOTAXIS.

Based on findings in the initial phase of the contract, studies of neutrophil function were continued in dogs receiving an increased dose of *E. coli* ($14 \times 10^9$, $20 \times 10^9$ and $30 \times 10^9$ bacteria per kilogram body weight), and at an elevated dose of irradiation (200 cGy). These increased concentrations and doses were selected by the AFRRI study director with the objective that a lethal model of irradiation induced-sepsis would magnify the effects of these treatments on the migration response. The results of these studies can be summarized as follows:

3.3.1 neutrophil chemotaxis in irradiated dogs - neutrophil migration in dogs receiving 200 cGy TBI was initially enhanced to the chemoattractant, normal dog serum, on day 1 post-TBI. This was followed by a continuous reduction in ability to migrate starting on day 3, and continuing through days 7, 10, and 14 days post-TBI. Migration capability returned toward normal starting on day 17 and continued to increase in magnitude of

migration ability through day 28, when the migration response was three (3) times greater than was seen with random migration.

3.3.2 neutrophil chemotaxis in E. coli dogs - neutrophil migration in dogs receiving E. coli at varying doses was initially enhanced and subsequently returned to normal. The pattern of these migration increases and the duration of the elevated responses were dependent upon the dose of E. coli.

3.3.2.1 E. coli at $14 \times 10^9$ - migration increased significantly on day 1 post-implant, and persisted at elevated migration levels through day 14 before returning to normal levels.

3.3.2.2 E. coli at $20 \times 10^9$ - 6 dogs studied in this group, and 4 dogs died by day 1. Data is insufficient to evaluate.

3.3.2.3 E. coli at $30 \times 10^9$ - 23 dogs studied in this group, of which 17 died in the first 3 days, and 6 dogs lived through 29 days post-implant. Migration was enhanced starting on day 1 and remained elevated through day 8 before returning to normal.

## 3.4 T-SUPPRESSOR CELL ASSAYS.

Studies of T-suppressor cell function were performed using lymphocytes from dogs receiving combined injury (TBI-SC and TBI-EC). The variability of the assay brought on by the constantly changing cell populations made interpretation of the results inconclusive. Additional studies will be required to elucidate this question.

## 3.5 OTHER ASSAYS.

Assays to evaluate the primary and secondary immune response to T-cell and B-cell dependent antigens were not conducted during this contract period. Further, studies of in vivo immune function performed to correlate with in vitro findings were also not performed in this contract period. These studies were not performed based on decisions made by the AFRRI study director to pursue other areas of interest, including evaluation of various animal models having greater potential for meeting the mission of AFRRI.

## SECTION 4

## MEETINGS AND PUBLICATIONS

### Publications and Presentations

The following list of papers and presentations resulted from studies performed on this contract.

### Presentations

1. Bowles, C. A., Fink, M., Gruber, D., MacVittie, T., McCoy, J., Walker, R., and Conklin, J. Variation in neutrophil responsiveness In Vitro following irradiation, surgical trauma and E. coli sepsis. Proc. RES Soc. 21: 431, 1984.

2. Bowles, C. A., Jerome, L., Linnekin, D., McCoy, J., Gruber, D., and MacVittie, T. Functional activity In Vitro of neutrophils from dogs receiving irradiation surgery and sepsis. Presented at: Immune Consequences of Thermal and Traumatic Injuries, Snowbird, Utah, 1984.

3. Bowles, C. A., Fink, M., Walker, R., Conklin, J., Linnekin, D., and MacVittie, T. Functional activity of canine lymphocytes and neutrophils following total body irradiation or E. coli sepsis. 2nd Intern. Symp. Pathophysio. Comb. Injury and Trauma, February, 1985.

### Papers

1. Conklin, J. J., Walker, R. I., Fink, M. P., Natanson, C., Parrillo, J. E., Danner, R. L., Bowles, C. A., Patchen, M., Gruber, D., and MacVittie, T. J. Pathophysiologic derangement in a septic canine model of combined injury (Submitted, 1986).

2. Bowles, C. A., Conklin, J., Walker, R. I., Jackson, W., Linnekin, D., and MacVittie, T. J. (In preparation).

### Meetings Attended

1. International Society of Experimental Hematology, London, 1983.

2. Reticuloendothelial Society, Montreal, Canada, 1984.

3. Symposium on Immune Consequences of Thermal and Traumatic Injuries, Snowbird, Utah, 1984.

4. Second International Symposium on Pathophysiology, Combined Injury and Traumas, Wintergreen, Virginia, 1985.

5. International Society of Experimental Hematology, Buffalo, New York, 1986.

Table 1. Experimental treatment groups for combined injury studies.

| Treatment Groups | No. of Dogs |
|---|---|
| Irradiation - 150 cGy | 6 |
| Irradiation - 200 cGy | 16 |
| *E. coli* Sepsis - $1 \times 10^9$ bacteria | 10 |
| $10 \times 10^9$ bacteria | 2 |
| $14 \times 10^9$ bacteria | 10 |
| $20 \times 10^9$ bacteria | 6 |
| $30 \times 10^9$ bacteria | 24 |
| $14 \times 10^9$ bacteria (killed) | 2 |
| $30 \times 10^9$ bacteria (killed) | 10 |
| Sterile Fibrin Clot | 13 |
| Irradiation (150 cGy) plus *E. coli* at $10 \times 10^9$ bacteria | 2 |
| Irradiation (150 cGy) plus *E. coli* at $1 \times 10^9$ bacteria | 4 |
| Irradiation (150 cGy) plus sterile fibrin clot | 6 |
| Irradiation (200 cGy) plus *E. coli* at $14 \times 10^9$ bacteria | 13 |
| Irradiation (200 cGy) plus sterile fibrin clot | 1 |
| TOTAL NUMBER DOGS STUDIED = | 125 |

Table 2. Assays of immune and inflammatory function.

A. Immune Function Assays

Lymphocyte blastogenesis - Stimulants of lymphocytes include concanavalin-A, phytohemagglutinin, pokeweed mitogen and allogenic cells.

T-Lymphocyte suppressor cell function - Suppression of normal T-lymphocytes evaluated after addition of leukocytes from experimental dogs.

Kinetics of lymphocyte responsiveness - Variability of lymphocyte response evaluated based on day of cell culture incubation and on dose of stimulating mitogen added to culture.

B. Inflammatory Cell (Neutrophil) Function

Adherence - Neutrophil adherence to glass and nylon wool was evaluated.

Fc Receptor expression - The number of cells expressing Fc receptors was evaluated.

Ingestion - The number of cells ingesting opsonized sheep erythrocytes was evaluated.

Migration - The ability of neutrophils to migrate randomly and in directed assays was determined.

Oxidative burst - The oxidative potential of neutrophils from experimental dogs was measured in nitroblue tetrazolium assays.

Microbial killing - The ability of neutrophils to kill S. typhimurium was determined following experimental treatment of the dogs.

C. Other Assays

Leukocyte inhibitory factor production studies were performed.

Macrophage function evaluation in adherence, and Fc receptor assays.

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